Author Response

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Author Response: Incident Open-Angle Glaucoma and Ocular Perfusion Pressure

In their letter, Leske et al. [1] mentioned our misinterpretation of their study on ocular perfusion pressure (OPP) and prevalent open-angle glaucoma (OAG) and our omission to incorporate their study on OPP and incident OAG in our recent publication on this topic.[2] The Barbados Eye Study published three studies regarding the association between OPP and OAG.[3–5] In their prevalent OAG report,[3] no adjustment for intraocular pressure (IOP) was made, and a significant association was found between diastolic OPP (DOPP) and OAG. Regrettably, this study was listed in the Discussion section of our article among the IOP-adjusted studies. Obviously, their findings, nevertheless, do not contradict the idea that a significant effect of OPP on OAG might be an artifact because IOP is part of OPP. One of their two reports from the Barbados Eye Study on OPP and incident OAG[4,5] was actually cited,[4] but we agree that this study should have been discussed in more detail. The authors thank Leske et al.[1] and the editor for providing the opportunity to rectify this omission.

In their incident OAG articles,[4,5] and also in the report from the Early Manifest Glaucoma Trial (EMGT),[6] OPP was presented in (two, three, or four) strata and a linear adjustment for IOP was added. A low DOPP was associated with incident OAG (and a low systolic OPP [SOPP] with OAG progression in the EMGT). The crucial question is now whether a linear adjustment for IOP is sufficient to remove all residual confounding. A linear adjustment bears the assumption that increases in IOP from, for example, 10 to 11 mm Hg and from 25 to 26 mm Hg are associated with an identical increase in OAG risk. Table 1 presents the results of a Cox regression similar to those presented in our article (based on 103 incident OAG cases and 3779 controls, and a mean follow-up of 9.8 years),[2] now addressing the simultaneous presence of baseline IOP as a linear variable and as a categorical variable, using tertiles. The lowest tertile served as the reference (as an upbeat to the OPP analyses, where the highest tertile is usually taken as the reference; OPP is essentially the difference between arterial blood pressure and IOP). Although, in our data, the IOP tertiles were not significant if a linear IOP adjustment was performed, the hazards ratio (HR) was highest for the highest tertile of IOP. Table 2 shows the corresponding analyses with the IOP in tertiles replaced by DOPP and SOPP, respectively. Now, the highest tertile served as the reference. As can be seen in this table, DOPP and SOPP were not associated with incident OAG and the HRs did not exceed that of the IOP in tertiles (Table 1).

To further address the hypothesis that OPP behaves like "noise added to IOP" in the analyses, we repeated the analyses as presented in Table 2 several times, with normally distributed random numbers instead of diastolic and systolic blood pressures. We used noise with a standard deviation of 10 mm Hg (similar to that of the diastolic blood pressure in our study) and 20 mm Hg (similar to that of the systolic blood pressure in our study). For both standard-deviation (SD) values, the analyses were repeated 10 times and were adjusted for age, sex, and baseline IOP as a linear variable. The median HR of the lowest tertile of the resampled DOPPs (diastolic blood pressure replaced by noise with 10 mm Hg SD) was 1.27 (range, 1.03–1.97); the median HR of the lowest tertile of the resampled SOPPs (systolic blood pressure replaced by noise with 20 mm Hg SD) was 0.99 (range 0.72–1.35). Obviously, the original HRs of the lowest tertiles of DOPP and SOPP (Table 2) are amply within these ranges. Interestingly, two of the DOPP resamplings had a lowest tertile that was significantly larger than 1.0 at $P < 0.05$ (HRs 1.93 [$P = 0.02$] and 1.97 [$P = 0.02$], respectively).

The additional analyses presented in this letter indicate that residual confounding can reveal a spurious association between a low DOPP and incident OAG, and thus the results reinforce the message of our article.[5] Obviously, this does not prove that perfusion does not play a role in other studies. Populations of other ethnicities may have different responses to low OPPs, and other populations may have on average higher IOPs and lower blood pressures, assuring more variability in OPP.

Table 1. Multivariate Cox Proportional Hazards Model Presenting the Risk of Developing OAG for linear IOP and Categorical IOP, in Tertiles with the Lowest Tertile as the Reference

	Hazards Ratio	95% CI	*P*
Age, y	1.08	1.05–1.11	<0.001
Sex, female	0.60	0.40–0.91	0.015
IOP, mm Hg	1.14	1.07–1.21	<0.001
IOP, middle tertile	0.90	0.44–1.82	0.76
IOP, highest tertile	1.54	0.75–3.19	0.24

Table 2. Multivariate Cox Proportional Hazards Model Presenting the Risk of Developing OAG for Linear IOP and Categorical DOPP and SOPP, in Tertiles with the Highest Tertile as the Reference

	Hazards Ratio	95% CI	*P*
Risk with DOPP			
Age, y	1.07	1.04–1.11	<0.001
Sex, female	0.59	0.39–0.89	0.012
IOP, mm Hg	1.17	1.12–1.22	<0.001
DOPP, middle tertile	0.72	0.40–1.27	0.25
DOPP, lowest tertile	1.11	0.68–1.83	0.68
Risk with SOPP			
Age, y	1.08	1.05–1.11	<0.001
Sex, female	0.59	0.39–0.90	0.013
IOP, mm Hg	1.17	1.12–1.22	<0.001
SOPP, middle tertile	0.88	0.52–1.49	0.64
SOPP, lowest tertile	1.21	0.74–1.98	0.44

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